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Herbal Formulations for The Antidiabetic Activity

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Abstract
Traditional Medicines derived from medicinal plants are used by about 60% of the world's population. This review focuses on Indian Herbal drugs and plants used in the treatment of diabetes, especially in India. Diabetes is an important human ailment afflicting many from various walks of life in different countries. In India it is proving to be a major health problem, especially in the urban areas. Though there are various approaches to reduce the ill effects of diabetes and its secondary complications, herbal formulations are preferred due to lesser side effects and low cost. A list of medicinal plants with proven antidiabetic and related beneficial effects and of herbal drugs used in treatment of diabetes is compiled. One of the etiologic factors implicated in the development of diabetes and its complications is the damage induced by free radicals and hence an antidiabetic compound with antioxidant properties would be more beneficial.

Keywords: medicinal plant, India, antidiabetic, diabetes

1. INTRODUCTION

In the last few years there has been an exponential growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Many traditional medicines in use are derived from medicinal plants, minerals and organic matter [1]. A number of medicinal plants, traditionally used for over 1000 years named rasayana are present in herbal preparations of Indian traditional health care systems [2]. In Indian systems of medicine most practitioners formulate and dispense their own recipes [3]. The World Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called as botanical garden of the world [3]. The current review focuses on herbal drug preparations and plants used in the treatment of diabetes mellitus, a major crippling disease in the world leading to huge economic losses.

1.1 Diabetes and Significance

Diabetes is a chronic disorder of carbohydrate, fat and protein metabolism characterized by increased fasting and post prandial blood sugar levels. The global prevalence of diabetes is estimated to increase, from 4% in 1995 to 5.4% by the year 2025. WHO has predicted that the major burden will occur in developing countries. Studies conducted in India in the last decade have highlighted that not only is the prevalence of diabetes high but also that it is increasing rapidly in the urban population [4]. It is estimated that there are approximately 33 million adults with diabetes in India. This number is likely to increase to 57.2 million by the year 2025.

Diabetes mellitus is a complex metabolic disorder resulting from either insulin insufficiency or insulin dysfunction. Type I diabetes (insulin dependent) is caused due to insulin insufficiency because of lack of functional beta cells. Patients suffering from this are therefore totally dependent on exogenous source of insulin while patients suffering from Type II diabetes (insulin independent) are unable to respond to insulin and can be treated with dietary changes, exercise and medication. Type II diabetes is the more common form of diabetes constituting 90% of the diabetic population. Symptoms for both diabetic conditions may include: (i) high levels of sugar in the blood; (ii) unusual thirst; (iii) frequent urination; (iv) extreme hunger and loss of weight; (v) blurred vision; (vi) nausea and vomiting; (vii) extreme weakness and tiredness; (viii) irritability, mood changes etc.

Though pathophysiology of diabetes remains to be fully understood, experimental evidences suggest the involvement of free radicals in the pathogenesis of diabetes [5] and more importantly in the development of diabetic complications [6– 8]. Free radicals are capable of damaging cellular molecules, DNA, proteins and lipids leading to altered cellular functions. Many recent studies reveal that antioxidants capable of neutralizing free radicals are effective in preventing experimentally induced diabetes in animal models [9, 10] as well as reducing the severity of diabetic complications.

For the development of diabetic complications, the abnormalities produced in lipids and proteins are the major etiologic factors. In diabetic patients, extra-cellular and long lived proteins, such as elastin, laminin, collagen are the major targets of free radicals. These proteins are modified to form glyco- proteins due to hyperglycemia. The modification of these proteins present in tissues such as lens, vascular wall and basement membranes are associated with the development of complications of diabetes such as cataracts, microangiopathy, atherosclerosis and nephropathy [11]. During diabetes, lipoproteins are oxidized by free radicals. There are also multiple abnormalities of lipoprotein metabolism in very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) in diabetes. Lipid peroxidation is enhanced due to increased oxidative stress in diabetic condition. Apart from this, advanced glycation end products

(AGEs) are formed by non-enzymatic glycosylation of proteins. AGEs tend to accumulate on long-lived molecules in tissues and generate abnormalities in cell and tissue functions [12, 13]. In addition, AGEs also contribute to increased vascular permeability in both micro and macrovascular structures by binding to specific macrophage receptors. This results in formation of free radicals and endothelial dys- function. AGEs are also formed on nucleic acids and histones and may cause mutations and altered gene expression.

As diabetes is a multifactorial disease leading to several complications and therefore demands a multiple therapeutic approach. Patients of diabetes either do not make enough insulin or their cells do not respond to insulin. In case of total lack of insulin, patients are given insulin injections. Whereas in case of those where cells do not respond to insulin many different drugs are developed taking into consideration possible disturbances in carbohydrate-metabolism. For example, to manage post-prandial hyper-glycaemia at digestive level, glucosidase inhibitors such as acarbose, miglitol and voglibose are used. These inhibit degradation of carbohydrates thereby reducing the glucose absorption by the cells. To enhance glucose uptake by peripheral cells biguanide such as metphormine is used. Sulphonylureas like glibenclamide is insulinotropic and works as secretogogue for pancreatic cells. Although several therapies are in use for treatment, there are certain limitations due to high cost and side effects such as development of hypoglycemia, weight gain, gastrointestinal disturbances, liver toxicity etc [14]. Based on recent advances and involvement of oxidative stress in complicating diabetes mellitus, efforts are on to find suitable antidiabetic and antioxidant therapy.

Medicinal plants are being looked up once again for the treatment of diabetes. Many conventional drugs have been derived from prototypic molecules in medicinal plants. Metformin exemplifies an efficacious oral glucose-lowering agent. Its development was based on the use of *Galega officinalis* to treat diabetes. *Galega officinalis* is rich in guanidine, the hypoglycemic component. Because guanidine is too toxic for clinical use, the alkyl biguanides synthalin A and synthalin B were introduced as oral anti-diabetic agents in Europe in the 1920s but were discontinued after insulin became more widely available. However, experience with guanidine and biguanides prompted the development of metformin. To date, over 400 traditional plant treatments for diabetes have been reported, although only a small number of these have received scientific and medical evaluation to assess their efficacy. The hypoglycemic effect of some herbal extracts has been confirmed in human and animal models of type 2 diabetes.

1.2 INDIAN MEDICINAL PLANTS WITH ANTIDIABETIC AND RELATED BENEFICIAL EFFECTS

There are many herbal remedies suggested for diabetes and diabetic complications. Medicinal plants form the main ingredients of these formulations. A list of medicinal plants with antidiabetic and related beneficial effects. [15].

1.2.1 Acacia arabica

It is found all over India mainly in the wild habitat. The plant extract acts as an antidiabetic agent by acting as secretagouge to release insulin. It induces hypoglycemia in control rats but not in alloxanized animals. Powdered seeds of Acacia arabica when administered (2,3 and 4 g/kg body weight) to normal rabbits induced hypoglycemic effect by initiating release of insulin from pancreatic beta cells [16].

1.2.2 Aegle marmelos

Administration of aqueous extract of leaves improves digestion and reduces blood sugar and urea, serum cholesterol in alloxanized rats as compared to control. Along with exhibiting hypoglycemic activity, this extract also prevented peak rise in blood sugar at 1h in oral glucose tolerance test [17].

1.2.3 Allium cepa

Various ether soluble fractions as well as insoluble fractions of dried onion powder show anti-hyperglycemic activity in diabetic rabbits. Allium cepa is also known to have antioxidant and hypolipidaemic activity. Administration of a sulfur containing amino acid from Allium cepa, S-methyl cysteine sulphoxide (SMCS) (200 mg/kg for 45 days) to alloxan induced diabetic rats significantly controlled blood glucose as well as lipids in serum and tissues and normalized the activities of liver hexokinase, glucose 6-phosphatase and HMG Co A reductase [18, 19]. When diabetic patients were given single oral dose of 50 g of onion juice, it significantly controlled post-prandial glucose levels [20].

1.2.4 Allium sativum

This is a perennial herb cultivated throughout India. Allicin, a sulfur-containing compound is responsible for its pungent odour and it has been shown to have significant hypo glycemic activity [21]. This effect is thought to be due to increased hepatic metabolism, increased insulin release from pancreatic beta cells and/or insulin sparing effect [22]. Aqueous homogenate of garlic (10 ml/kg/day) administered orally to sucrose fed rabbits (10 g/kg/day in water for two months) significantly increased hepatic glycogen and free amino acid content, decreased fasting blood glucose, and triglyceride levels in serum in comparison to sucrose controls [23].

S-allyl cystein sulfoxide (SACS), the precursor of allicin and garlic oil, is a sulfur containing amino acid, which controlled lipid peroxidation better than glibenclamide and insulin. It also improved diabetic conditions. SACS also stimulated in

vitro insulin secretion from beta cells isolated from normal rats [24]. Apart from this, Allium sativum exhibits anti-microbial, anticancer and cardioprotective activities.

1.2.5 Aloe vera and Aloe barbadensis

Aloe, a popular houseplant, has a long history as a multi- purpose folk remedy. The plant can be separated into two basic products: gel and latex. Aloe vera gel is the leaf pulp or mucilage, aloe latex, commonly referred to as "aloe juice," is a bitter yellow exudate from the pericyclic tubules just beneath the outer skin of the leaves. Extracts of aloe gum effectively increases glucose tolerance in both normal and diabetic rats [25]. Treatment of chronic but not single dose of exudates of Aloe barbadensis leaves showed hypo- glycemic effect in alloxanized diabetic rats. Single as well as chronic doses of bitter principle of the same plant also showed hypoglycemic effect in diabetic rats. This action of Aloe vera and its bitter principle is through stimulation of synthesis and/or release of insulin from pancreatic beta cells [26]. This plant also has an anti-inflammatory activity in a dose dependent manner and improves wound healing in diabetic mice [27].

***1.2.6 Azadirachta indica*:**

Hydroalcoholic extracts of this plant showed anti- hyperglycemic activity in streptozotocin treated rats and this effect is because of increase in glucose uptake and glycogen deposition in isolated rat hemidiaphragm [28, 29]. Apart from having anti-diabetic activity, this plant also has anti-bacterial, antimalarial, antifertility, hepatoprotective and antioxidant effects [30].

1.2.7 Caesalpinia bonducella

Caesalpinia bonducella is widely distributed throughout the coastal region of India and used ethnically by the tribal people of India for controlling blood sugar. Both the aqueous and ethanolic extracts showed potent hypoglycemic activity in chronic type II diabetic models. These extracts also increased glycogenesis thereby increasing liver glycogen content [31]. Two fractions BM 169 and BM 170 B could increase secretion of insulin from isolated islets. The aqueous and 50% ethanolic extracts of *Caesalpinia bonducella* seeds showed antihyperglycemic and hypolipidemic activities in streptozotocin (STZ)-diabetic rats [32]. The antihyperglycemic action of the seed extracts may be due to the blocking of glucose absorption. The drug has the potential to act as antidiabetic as well as antihyperlipidemic [33].

1.2.8 Capparis decidua

This is found throughout India, especially in dry areas. Hypoglycemic effect was seen in alloxanized rats when the rats were fed with 30% extracts of *Capparis decidua* (*C. decidua*) fruit powder for 3 weeks. This extract also reduced alloxan induced lipid peroxidation significantly in erythrocytes, kidney and heart. *C. decidua* was also found to alter superoxide dismutase and catalase enzyme levels to reduce oxidative stress [34]. *C. decidua* additionally showed hypolipidaemic activity [35].

1.2.9 Coccinia indica

Dried extracts of Coccinia indica were administered to diabetic patients for 6 weeks. These extracts restored the activities of enzyme lipoprotein lipase (LPL) that was reduced and glucose-6- phosphatase and lactate dehydrogenase, which were raised in untreated diabetics [36]. Oral administration of 500 mg/kg of C. indica leaves showed significant hypoglycemia in alloxanized diabetic dogs and increased glucose tolerance in normal and diabetic dogs.

1.2.10 Mangifera indica

The leaves of this plant are used as an antidiabetic agent in Nigerian folk medicine, although when aqueous extract given orally did not alter blood glucose level in either normoglycemic or streptozotocin induced diabetic rats. However, antidiabetic activity was seen when the extract and glucose were administered simultaneously and also when the extract was given to the rats 60 min before the glucose. The results indicate that aqueous extract of *Mangifera indica* possess hypoglycemic activity. This may be due to an intestinal reduction of the absorption of glucose [*38*].

***1.2.11 Momordica charantia*:**

Momordica charantia is commonly used as an antidiabetic and antihyperglycemic agent in India as well as other Asian countries. Extracts of fruit pulp, seed, leaves and whole plant was shown to have hypoglycemic effect in various animal models. Polypeptide p, isolated from fruit, seeds and tissues of *M. charantia* showed significant hypoglycemic effect when administered subcutaneously to langurs and humans [39]. Ethanolic extracts of *M. charantia* (200 mg/kg) showed an antihyperglycemic and also hypoglycemic effect in normal and STZ diabetic rats. This may be because of inhibition of glucose-6-phosphatase besides fructose-1, 6- biphosphatase in the liver and stimulation of hepatic glucose- 6-phosphate dehydrogenase activities [40].

1.2.12 Ocimum sanctum

It is commonly known as Tulsi. Since ancient times, this plant is known for its medicinal properties. The aqueous extract of leaves of Ocimum sanctum showed the significant reduction in blood sugar level in both normal and alloxan induced

diabetic rats [41]. Significant reduction in fasting blood glucose, uronic acid, total amino acid, total cholesterol, triglyceride and total lipid indicated the hypoglycemic and hypolipidemic effects of tulsi in diabetic rats [42]. Oral administration of plant extract for 30 days led to decrease in the plasma glucose level by approximately 9.06 and 26.4% on 15 and 30 days of the experiment respectively. Renal glycogen content increased 10-fold while skeletal muscle and hepatic glycogen levels decreased by and 75% respectively in diabetic rats as compared to control [43]. This plant also showed antiasthemitic, antistress, anti- bacterial, antifungal, antiviral, antitumor, gastric antiulcer activity, antioxidant, antimutagenic and immunostimulant activities.

1.2.13 Phyllanthus amarus

It is a herb of height up to 60 cm, from family Euphorbiaceae. It is commonly known as Bhuiamala. It is scattered throughout the hotter parts of India, mainly Deccan, Konkan and south Indian states. Traditionally it is used in diabetes therapeutics. Methanolic extract of *Phyllanthus amarus* was found to have potent antioxidant activity. This extract also reduced the blood sugar in alloxanized diabetic rats [44]. The plant also shows anti-inflammatory, antimutagenic, anticarcinogenic, antidiarrhoeal activity.

***1.2.14 Pterocarpus marsupium*:**

It is a deciduous moderate to large tree found in India mainly in hilly region. Pterostilbene, a constituent derived from wood of this plant caused hypoglycemia in dogs [45, 46] showed that the hypoglycemic activity of this extract is because of presence of tannates in the extract. Flavonoid fraction from Pterocarpus marsupium has been shown to cause pancreatic beta cell regranulation [47]. It obtained from this plant showed antihyperlipidemic activity [48]. Epicatechin, its active principle, has been found to be insulinogenic, enhancing insulin release and conversion of proinsulin to insulin in vitro. Like insulin, epicatechin stimulates oxygen uptake in fat cells and tissue slices of various organs, increases glycogen content of rat diaphragm in a dose-dependent manner [49].

1.2.15 Trigonella foenum graecum

It is found all over India and the fenugreek seeds are usually used as one of the major constituents of Indian spices. 4-hydroxyleucine, a novel amino acid from fenugreek seeds increased glucose stimulated insulin release by isolated islet cells in both rats and humans [50]. Oral administration of 2 and 8 g/kg of plant extract produced dose dependent decrease in the blood glucose levels in both normal as well as diabetic rats [51]. Administration of fenugreek seeds also improved glucose metabolism and normalized creatinine kinase activity in heart, skeletal muscle and liver of diabetic rats. It also reduced hepatic and renal glucose-6-phosphatase and fructose –1,6-biphosphatase activity [52]. This plant also shows antioxidant activity [53, 54].

***1.2.16 Tinospora cordifolia*:**

It is a large, glabrous, deciduous climbing shrub belonging to the family *Menispermaceae*. It is widely distributed throughout India and commonly known as Guduchi. Oral administration of the extract of *Tinospora cordifolia* (*T. cordifolia*) roots for 6 weeks resulted in a significant reduction in blood and urine glucose and in lipids in serum and tissues in alloxan diabetic rats. The extract also prevented a decrease in body weight. [55] *T. cordifolia* is widely used in Indian ayurvedic medicine for treating diabetes mellitus [56–58]. Oral administration of an aqueous *T. cordifolia* root extract to alloxan diabetic rats caused a significant reduction in blood glucose and brain lipids. Though the aqueous extract at a dose of 400 mg/kg could elicit significant anti- hyperglycemic effect in different animal models, its effect was equivalent to only one unit/kg of insulin [59]. It is reported that the daily administration of either alcoholic or aqueous extract of *T. cordifolia* decreases the blood glucose level and increases glucose tolerance in rodents [60].

2. Conclusion

Herbal therapy for diabetes has been followed all over the World successfully. Herbs are used to manage Type 1 and Type II diabetes and their complications. For this, therapies developed along the principles of western medicine (allopathic) are often limited in efficacy, carry the risk of adverse effects, and are often too costly, especially for the developing world. The above-mentioned plants have been considered for their possible hypoglycemic actions and the researchers have carried out some preliminary investigations. Scientific validation of several Indian plant species has proved the efficacy of the botanicals in reducing the sugar level could be considered as of possible therapeutic value. Thus many different plants have been used individually or in formulations for treatment of diabetes.

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